REMARKS

In the communication mailed December 23rd, the Examiner has rejected claims 1 through 6 under the judicially created doctrine of obviousness-type double patenting over claim 1 of U.S. Pat. 6,627,634 B2 (the '634 patent). Additionally, the Examiner has provisionally rejected claims 1 through 6 of the instant application over claims 1 through 6 of co-pending application S.N. 10/016,280 (the '280 application). Reconsideration of such rejections is respectfully requested.

The Examiner compares C of the '634 patent with Rb of the subject application. Within the broad definition of C in the '634 patent, only the part referring to a C2-4-alkyl-NR4-group wherein the C2-4 alkyl moiety is substituted from position 2 (that is, one of positions 2, 3 or 4 must be substituted) can be compared with Rb in claim 1 of the subject application. This is the terminal group in the side chain attached to position 6 of the quinazoline (X is N).

Rb of the subject application is defined to be an amino group being either substituted by methyl or ethyl **and** by a second substituent selected from lower alkyl, methoxyethyl, cyclopropyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrofuranyl-methyl or tetrahydropyranyl-methyl,

or Rb can be bis(methoxyethyl)amino or morpholino.

The corresponding definition of C in claim 1 of the '634 patent is as follows:
a C_{2-4}-alkyl-NR_4-group, wherein the C_{2-4}-alkyl moiety is substituted from position 2 by an (R_4NR_6), **R_6O,** R_6S, R_6SO, R_6SO_2, or **2-oxo-morpholino** group, wherein the 2-oxo-morpholino moiety is optionally substituted by one or two C_{1-2}-alkyl groups, wherein.....
R4 is a hydrogen atom or a C1-4 alkyl group; .....
R6 is a 2-**oxo**tetrahydrofuranyl-3-yl, 2-**oxo**tetrahydrofuranyl-4-yl, 2-**oxo**tetrahydropyrany-4-yl, or 2-**oxo**tetrahydropyrany-5-yl group optionally substituted by one or two C1-2-alkyl groups

Comparing both definitions, it is clear that the substituents (R_4NR_6), R_6S, R_6SO, R_6SO_2 are remote and cannot be effectively argued to be obvious variants: the first one would result a dialkylamino group substituted within an alkyl moiety substituted by dialkylamino (R_4NR_6 -> C_{2-4}-alkyl-NR_4-). Nothing similar is within the definition of Rb in the subject application. Furthermore, no sulfur containing substituents are in the definition of Rb. As a third point, the presence of R6 is mandatory.

R_6O as substituent is defined in the '634 patent to cover **only lactone groups** (cyclic esters) since the **oxo**-tetrahydrofuran- and tetrahydropyran rings contain a carbonyl group within the ring attached to the ring oxygen atom, resulting in the structural element **-C(O)-O-.** The same applies to the oxo-morpholino group.

Rb of the subject application **does not cover lactones.** The corresponding groups are cyclic ethers. This difference results in different activity. The lactones disclosed in the '624 patent are hydrolyzed easily in plasma, and are therefore suitable for topical or inhalative administration. They are active on skin or in the lungs, but are inactivated rather quickly when absorbed. Accordingly, the compounds of the '634 patent have the advantage of less systemic side effects, e.g., toxicity. In contrast, the cyclic ethers of the subject application are stable in plasma and suitable for oral or parenteral administration. In cancer therapy, this is desirable since these are the usual routes of administration, and therefore combination with other agents is possible.

Concerning the provisional double-patenting rejection over the '280 application, the Examiner's attention is respectfully drawn to the Declaration of Frank Himmelsbach signed on 8 April, 2004. Paragraph 5 and the first table within the declaration show that the compounds of the subject application are highly active dual inhibitors both of EGFR-kinase and HER2 tyrosine kinase.

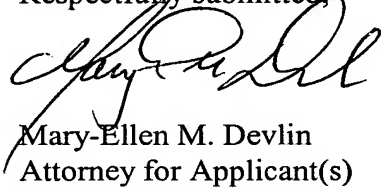
Paragraph 6 and the second table refer to a comparison between the frontrunner compound of the subject application, that is Ex. 1(10) and the most similar prior art compound, that is Ex. 3(30) of the '280 application. The only structural difference is that Ex. 1(10) possesses a dimethylamino group for Rb whereas Ex. 3(30) has diethylamino for this group, resulting an

about 10-fold better activity both for inhibition of EGF-R kinase and HER2 tyrosine kinase. This already explained and reviewed in the response to Office Action filed on 8 April 2004.

In view of the foregoing, it is respectfully submitted that claims 1 through 3 and claims 21 through 23 are patentable over both the '634 patent and the '280 application. Accordingly, no terminal disclaimers are warranted.

Allowance of the pending claims herein is respectfully requested and an early issuance of a notice of allowance is earnestly solicited.

Respectfully submitted,



Mary-Ellen M. Devlin
Attorney for Applicant(s)
Reg. No. 27,928

Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877
Tel: (203) 798-4866

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Mary-Ellen M. Devlin, Reg. No. 27,928